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P4.07: EFFECTS OF ANTI-HYPERTENSIVE TREATMENT ON FUNCTIONAL AND STRUCTURAL COMPONENTS OF LARGE ARTERY STIFFNESS IN A RODENT MODEL OF TYPE I DIABETES

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Objectives: Autosomal dominant polycystic kidney disease (ADPKD) is due to mutations in genes PKD1 and PKD2 encoding polycystin-1 and -2, which transduce flow variations into cellular signals in the renal epithelium but also in vascular endothelium. However, the impact of polycystin deficiency on the release of endothelium-derived factors during flow variations is unknown.

Methods: In 21 normotensive ADPKD patients with normal kidney function and 21 control subjects, radial artery diameter and blood flow were measured during hand skin heating and post-ischemic hyperaemia. Local blood samples were drawn during heating to quantify plasma nitrite, indicator of nitric oxide (NO) availability, epoxyeicosatrienoic acids (EETs) and endothelin-1.

Results: Basal inflammatory and oxidative stress markers were similar between groups. Flow-mediated dilatation was lower in ADPKD patients than in controls during heating (16.1 ± 1.1 vs. $23.2 \pm 1.0\%$), as confirmed by their downward shift of the diameter-shear stress relationship, but not during post-ischemic hyperaemia, and without difference in endothelium-independent dilatation to glyceryl trinitrate. Nitrite increased during heating in controls but not in patients (30 ± 10 vs. -16 ± 8 nmol/L). Plasma EETs tended to increase in controls but not in patients, without difference in endothelin-1 reduction. Intra-brachial infusion of dopamine (0.25 - 0.5 mg/kg/min) during heating induced a dose-dependent upward shift of the diameter-shear stress relationship in ADPKD patients and restoration of NO release.

Conclusions: ADPKD patients display a loss of NO release and subsequent reduction in endothelium-dependent dilatation during sustained flow increase. The prevention of this alteration by dopamine may help to reduce the high prevalence of cardiovascular diseases in ADPKD.

P4.06

ARTERIAL STIFFNESS CORRELATES WITH VITAMIN D DEFICIENCY IN HYPERTENSIVE PATIENTS WITH STAGE 3 CHRONIC KIDNEY DISEASE INDEPENDENTLY OF BLOOD PRESSURE

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Objectives: To assess the prevalence of vitamin D deficiency and hyperparathyroidism as well as their relationship to blood pressure and arterial stiffness in hypertensive patients with stage 3 chronic kidney disease (CKD).

Methods: Cross-sectional study that included 134 treated hypertensives (76 women, 56,7%) with stage 3 CKD (eGFR 49.2 ml/min, $SD \pm 8$) without previous vitamin D supplementation treatment. Standard clinical care was performed including ECG, microalbuminuria and usual laboratory parameters. Arterial stiffness was measured by brachial oscillometry with the validated Mobil-O-Graph® device. Normal values for vitamin D and PTH were set as 30 ng/ml and 65 pg/ml, respectively.

Results: The mean age was 73.0 years ($SD \pm 10$) with office BP of $131/75$ mmHg ($SD \pm 17/11$). The prevalence of vitamin D deficiency was 89% (mean: 19 ng/ml ($SD \pm 10$)), secondary hyperparathyroidism was observed in 49% of patients (mean: 70.5 pg/ml ($SD \pm 10$)), 84 (62.7%) patients had a pulse wave velocity (PWV) over 10 m/sec (mean 10.7 m/sec, ($SD \pm 1.8$)). In bivariate analysis PWV correlated best with age ($r = 930$; $p < 0.0001$), followed by SBP ($r = 345$; $p < 0.0001$), vitamin D ($r = 310$; $p < 0.0001$), PTH, calcium, fosforous and ventricular mass (CORNELL). In multiple lineal regression analysis, only age, SBP and vitamin D remained significantly associated with arterial stiffness. In logistic regression with presence /absence of PWV ≥ 10 m/sec as dependent variable, male gender, age, elevated SBP and vitamin D categorized in tertiles were significantly related to increased PWV.

Conclusions: In hypertensive patients with stage 3 CKD vitamin D deficiency is associated to increased PWV independently of blood pressure, gender and age.

P4.07

EFFECTS OF ANTI-HYPERTENSIVE TREATMENT ON FUNCTIONAL AND STRUCTURAL COMPONENTS OF LARGE ARTERY STIFFNESS IN A RODENT MODEL OF TYPE I DIABETES

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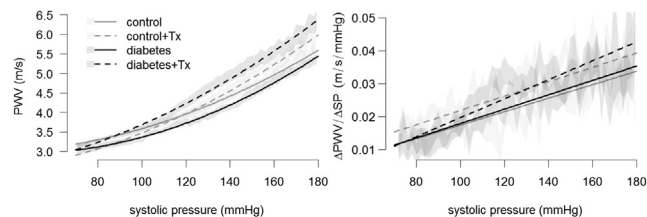
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Objectives: Diabetes is associated with cardiovascular risk and increased arterial stiffness. Whether large artery stiffness is associated with diabetes *per se* or concomitant hypertension is currently unknown.

Methods: Male, Wistar rats (6 weeks) were divided into control ($n = 8$), control with anti-hypertensive treatment (telmisartan, 10 mg/kg/day, $n = 8$), induced diabetes (intraperitoneal streptozotocin, 50 mg/kg, confirmed by blood glucose measurement, $n = 12$) and diabetes with anti-hypertensive treatment ($n = 12$). At 18 weeks, rats were anaesthetised (urethane, 1.3 g/kg) and aortic pulse wave velocity (aPWV, aortic stiffness) measured invasively across a full range of physiological arterial pressure (intravenous phenylephrine, sodium nitroprusside, 30 μ g/kg/min). Passive (elastin, collagen) and active (endothelial, smooth muscle function) components of stiffness were quantified using tensile testing and myography.

Results: Conscious, systolic blood pressure was high in both control and diabetic animals (142 ± 16 , 132 ± 22 mmHg) compared to control and diabetic animals on anti-hypertensive therapy (105 ± 11 , 119 ± 14 mmHg, $p < 0.01$). Diabetic animals had marginally but significantly lower aPWV across all pressures (Figure). Anti-hypertensive treatment increased aPWV in controls and diabetic animals, but increased the pressure dependency of aPWV (Figure). There was no difference in endothelial dependent or independent vasorelaxation. Sensitivity to phenylephrine (vasoconstriction) was less in diabetic animals ($p < 0.05$). Anti-hypertensive therapy caused a rightward shift in the aortic stress-strain curve ($p < 0.001$).

Conclusions: Diabetes appeared to have a small but positive effect on arterial stiffness when studied independent of blood pressure. However, high blood pressure decreased the artery's ability to respond to acute pressure changes, possibly due to remodelling of passive aortic wall components.



P4.08

INSULIN RESISTANCE IS THE MAIN TARGET IN PREVENTING ACCELERATING ARTERIAL AGING

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Objectives: Increased arterial stiffness (AS) is the most prominent feature of arterial aging. It has been shown an association of AS not only with age, but also with insulin resistance (IR). Leukocyte telomere length (TL) has been proposed as an independent predictor of CVD. The origin of the association between TL and CVD may be related to its effect on AS. TL attrition is accelerated by chronic inflammation and oxidative stress associated with IR. We assessed the hypothesis that TL attrition under the influence of IR leads to arterial stiffening.

Methods: The study group included 99 subjects mean age 51.3 ± 12.3 years, free of known CVD, 20 subjects had T2DM. Serum fasting glucose (FG), insulin, Hb1Ac were determined using routine laboratory methods. HOMA-IR was calculated as fasting insulin (mU/ml) x FG (mmol/l)/22.5. TL was determined by PCR. AS was evaluated by measuring aortic pulse wave velocity (PWV) with the help of SphygmoCor (AtCor Medical).

Results: Through multiple linear regression analysis, PWV was found to be independently and positively associated with age, FG, Hb1Ac, independently and negatively associated with TL (see table 1). TL was found to be independently and negatively associated with age, HOMA-IR (see table 2). In all subjects age, TL, FG, Hb1Ac predicted 43% of the variance in PWV ($p < 0.0001$). Age, HOMA-IR predicted 24% of the variance in TL ($p < 0.0001$).